UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,009	11/28/2001	Marina Konopleva	UTSC:652US	7245

7590 07/03/2006

Priya D. Subramony
Fulbright & Jaworski L.L.P.
600 Congress Avenue, Suite 2400
Austin, TX 78701

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,009	KONOPLEVA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Informalities

Claims 1-66 are currently pending and are the subject of this Office Action. The *Ex Parte* Quayle Action mailed November 30, 2005 is hereby **vacated** and prosecution is reopened in order to examine the full scope of the claimed invention.

Election/Restrictions

The species election requirement as set forth in the Office Action mailed on July 14, 2004 is hereby **withdrawn**. The search of the present invention has been expanded to include: 1) other species of leukemia cells recited in claim 8; 2) all species of solid tumor cells recited in claim 10; and 3) other species of chemotherapeutic agents recited in claims 21-24, 44, 48, 52, and 56.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-33, 36-37, 40-41, 44-45, 48-49, 52-53 and 56-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods comprising administration of a "CDDO-compound" and a chemotherapeutic agent. The only examples of CDDO-compounds provided in the specification are CDDO and methyl-CDDO (page 4, lines 12-14). CDDO is defined in the specification as 2-cyano-3,12-dioxoolean-1,9-diene-28-oic acid (p. 15, line 20) and methyl-CDDO is defined as the C-28 methyl ester of CDDO (p. 16, line 15). Methods of synthesizing CDDO and methyl-CDDO are provided in the specification at pages 16 and 17. Nowhere, however, does the specification contemplate or describe the structural features of other "CDDO-compounds" other than CDDO and methyl-CDDO.

The instant claims are broad, being drawn to the use of "a CDDO-compound" in general, however applicants have not provided any structural features or any other means for the skilled artisan to appreciate exactly what compounds are considered to be CDDO-compounds. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004). Applicants have provided no means for the skilled artisan to visualize or recognize what compounds, aside from CDDO and methyl-CDDO, are included in the phrase "CDDO-compounds."

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 recites the limitation "CDDO" in line 2. This limitation renders the claim 1 and all claims dependent from claim 1 indefinite because the first recitation of an abbreviation in the claims must include the expanded meaning within the first claim wherein the abbreviation is used.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh *et al.* (C22).

Suh *et al.* disclose that CDDO inhibits cell proliferation of several cancer cell lines *in vitro* (see especially Table 1, p. 337). It is further disclosed that CDDO acts synergistically with LG100268 to induce differentiation of 3T3-L1 fibroblasts (Fig. 2, p. 339).

Thus, the instantly claimed method of inducing differentiation in a cell with a CDDO-compound and a chemotherapeutic agent would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The motivation to

do so is found in the Suh reference wherein it is demonstrated that CDDO acts synergistically with LG100268 to induce differentiation.

Claims 11-12, 22-23, 33-34, 36-38, 40-42, 44-46, 48-50, 52-54 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.* (C25) in view of Elstner *et al.* (Proc. Natl. Acad. Sci. USA, 1998, v. 95, pp. 8806-8811).

Wang *et al.* disclose that CDDO is a novel synthetic triterpenoid (Abstract) that induces differentiation both as a single agent and synergistically with an RXR-specific ligand (second column, p. 1551). It is further disclosed that the adipogenic effect of CDDO is due to its binding to PPARγ (second column, p. 1551).

Elstner *et al.* disclose that ligands for PPARγ and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells *in vitro* and *in vivo* (Abstract). The anitdiabetic drug, troglitazone (TGZ), a synthetic-specific ligand of PPARγ was shown to act synergistically with the retinoic acid receptor (RAR) specific ligand all-*trans*-retinoic acid (ATRA) to decrease colony formation of MCF7 cells *in vitro* (Fig. 3, p. 8808) and to decrease the size of MCF7 tumors in mice (Fig. 6, p. 8809).

Given the disclosures of Wang and Elstner, the skilled artisan would have been motivated to combine CDDO with other chemotherapeutic agents for the treatment of cancer with at least a reasonable expectation of success. The motivation to combine the references is found in Elstner *et al.* who state that:

> Taken together, the combination of ligands for PPARγ and RAR inhibited growth and induced apoptosis of breast cancer cells *in vitro* and *in vivo*; this combination may provide nontoxic and selective therapy for human breast cancers. Elstner (1998) at second column, last paragraph, p. 8810.

From the combined references it is clear that PPARγ ligands and RAR ligands act in a synergistic manner when used as a combined therapy in the treatment of breast cancer.

Thus, the instant claims would have been *prima facie* obvious to the skilled artisan at the time the invention was made.

Claims 1-2, 6-8, 21, 33-34 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh *et al.* and Ito *et al.* (C28) in view of Al-alami *et al.* (Leukemia Research, 1998, v. 22, pp. 939-945) and Lieu *et al.* (Biochemical Pharmacology, 1997, v. 53, pp. 1587-1596).

Suh *et al.* disclose that CDDO inhibits cell proliferation of U937 and HL-60 leukemia cells *in vitro* (Table 1).

Ito *et al.* disclose that CDDO induces the apoptosis of U-937 and HL-60 human myeloid leukemia cells (Abstract; Fig. 1; Fig. 2).

Al-alami *et al.* demonstrate that the chemotherapeutic drug taxol increases apoptosis (Fig. 1) as well as decreases the cell proliferation (Fig. 3) of U-937 leukemia cells

Lieu *et al.* discloses that taxol induces mitotic block and apoptosis of HL-60 leukemia cells (Abstract; Fig. 5). Taxol was also shown to demonstrate a cytotoxic effect on HL-60 cells *in vitro* (Fig. 1).

It would have been *prima facie* obvious to the skilled artisan at the time the invention was made to combine CDDO and a chemotherapeutic agent, such as taxol, in methods to induce cytotoxicity and apoptosis of leukemia cells because both agents were known in the art to be useful for these purposes. The skilled artisan would be imbued with at least a reasonable expectation of success because both agents were known in the art to be individually effective at inducing cytotoxicity and apoptosis of leukemia cells.

Claims 1-2, 6, 9-10, 21, and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh *et al.* in view of Kurbacher *et al.* (Cancer Letters, 1996, v. 103, pp. 183-189).

Suh *et al.* disclose that CDDO inhibits cell proliferation of MCF-7 and MDA-MB-231 breast cancer cells *in vitro* (Table 1).

Kurbacher *et al.* disclose that taxol demonstrates cytotoxicity to MCF-7 and MDA-MB-237 breast cancer cells *in vitro* (Fig. 3A and 3C).

It would have been *prima facie* obvious to the skilled artisan at the time the invention was made to combine CDDO and a chemotherapeutic agent, such as taxol, in a method to induce cytotoxicity because both agents were known in the art to be useful for this purpose.

With regard to the above rejections under 35 U.S.C. § 103, it is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Examiner
Art Unit 1614

June 14, 2006

6/26/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER